UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,784	08/22/2005	Ayyappan K. Rajasekaran	UCLA-005	7707

24353 7590 03/18/2008

BOZICEVIC, FIELD & FRANCIS LLP
1900 UNIVERSITY AVENUE
SUITE 200
EAST PALO ALTO, CA 94303

EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
03/18/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,784	RAJASEKARAN ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *3 and 6-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4 and 5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/4/06;6/15/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of group I, claims 1-2, a nucleic acid encoding Na, K-ATPase, in the reply filed on 06/15/07 is acknowledged.

The traversal is on the ground(s) that it would not be a burden to search all the claims together.

This is not found to be persuasive for the following reasons:

According to PCT Rule 13.2, unity of invention exists only when the shared same or corresponding technical feature is a contribution over the prior art. The inventions listed as groups 1-12 do not relate to a single general inventive concept because they lack the same or corresponding special technical feature. The shared technical feature of group 1, Na,K-ATPase alpha and beta subunits are known in the art, as disclosed in the specification (p.1, paragraph before last, p.2, paragraph under Biological sequences).

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, group I, claims 1-2, 4-5, a nucleic acid encoding Na,K-ATPase, are examined in the instant application.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2, 4-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-2, 4-5 are indefinite, for the use of the relative term "high" and "low" in claim 1. The term "high" and "low" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

To comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, the specification must enable one skilled in the art to make and use the claimed invention without undue experimentation. The claims are evaluated for enablement based on the Wands analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731,8 USPQ2d 1400 (Fed.Circ.1988) as follows: (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The specification discloses that high level of human Na,K-ATPase alpha **protein** subunit and low level of the beta protein subunit are found in human bladder cancer tissues between 1985 and 1995, and lead to increased risk of recurrence, as shown by multivariate logistic regression, or Cox multivariate analysis (p.17, last paragraph bridging p.18, p.24, second paragraph). The specification, however, discloses that when other covariates such as gender, age, grade and stage were added into the regression model, the expression levels **lost significance** (p.24, second paragraph). The specification discloses that both the NA,K-ATPase alpha-1 and beta-1 protein subunits are found in the human bladder (p. 21, last paragraph).

The specification, however, does not have any data or objective evidence that high level of Na,K-ATPase alpha **nucleic acid** subunit and low level of the beta nucleic acid subunit are found in bladder cancer tissues, and correlated with risk of bladder recurrence, nor risk of malignancy.

"Risk of malignancy" as claimed in claims 1-2, 4-5 encompasses risk of any cancer, including bladder cancer.

1. Claims 1-2, 4-5 are rejected under 112, first paragraph, for lack of a method for **predicting risk of any cancer, including bladder cancer.**

One cannot predict that high level of Na,K-ATPase alpha nucleic acid subunit and low level of its beta nucleic acid subunit are indicative of risk of any cancer, including bladder cancer, because the levels of the nucleic acids encoding Na,K-ATPase alpha and beta subunits in bladder cancer tissue cannot be predicted, based solely on the level of the encoded Na,K-ATPase alpha and beta subunits. Greenbaum *et al,* 2003 (Genome Biology, Vol. 4, Issue 9, pages 117.1-117.8) cautions against assuming that mRNA levels are generally correlative of protein levels.

To date, however, there have been only a handful of efforts to find **correlations between mRNA and protein expression levels**, most notably in human cancers and yeast cells, and, for the most part, they have reported only minimal and/or limited correlations (p.117.3, column 2). The reference further teaches (page 117.4, col 2) that there are presumably at least three reasons for the poor correlations generally reported in the literature between the level of mRNA and the level of protein, and these may not be mutually exclusive. First, there are many complicated and varied post-transcriptional mechanisms involved in turning mRNA into protein that are not yet sufficiently well defined to be able to compute protein concentrations from mRNA; second, proteins may differ substantially in their *in vivo* half lives; and/or third, there is a significant amount of error and noise in both protein and mRNA experiments that limit our ability to get a clear picture. The reference further notes (page 117.6, page col 2) that to be fully able to understand the relationship between mRNA and protein abundances, the dynamic processes involved in protein synthesis and degradation have to be better understood. Similarly, Fu et al 1996 (EMBO Journal, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Yokota, J et al, 1988 (Oncogene, Vol.3, pp. 471-475) teach that the retinoblasma (RB) 115 kD protein is not detected in all nine cases of lung small-cell carcinoma, with either normal or abnormal size mRNA, whereas the RB protein is detected in three of four adenocarcinomas and all three squamous cell carcinomas and one of two large cell carcinomas expressing normal size RB mRNA. Zimmer, 1991 (Cell Motility and the Cytoskeleton, vol. 20, pp. 325-337) teaches that there is no correlation between the mRNA level of calcium-modulated protein S100 alpha and

the protein level, indicating that S100 protein is post-transcriptionally regulated. Hell et al, 1995 (Laboratory Investigation, Vol. 73, pp. 492-496) teach that cells in all types of Hodgkin's disease exhibited high levels of bcl-2 mRNA, while the expression of the Bcl-2 protein was not homogenous to said cells. Guo et al, 2002 (Journal of Pharmacology and Experimental Therapeutics, vol. 300, pp. 206-212) teach that Oatp2 mRNA levels did not show a correlation with Oatp2 protein levels, suggesting that regulation of the Oatp2 protein occurs at both the transcriptional and post-translational level. For the above reasons, one of skill in the art would not be able to predict the relative levels of the nucleic acids encoding Na,K-ATPase alpha and beta subunits in bladder cancer tissue. Consequently, one cannot predict that high level of Na,K-ATPase alpha nucleic acid subunit and low level of its beta nucleic acid subunit are indicative of risk of any cancer, including bladder cancer.

Further, one cannot predict that high level of Na,K-ATPase alpha nucleic acid subunit and low level of the beta nucleic acid subunit are indicative of risk of any cancer, including bladder cancer, based on the disclosed statistical prediction of recurrence of bladder cancer, because, as admitted by the specification, when important factor such as gender, age, grade and stage were added into the regression model, the **results are not significant** (the instant specification, p.24, second paragraph).

Further, even if there were a correlation between the level of the encoding mRNAs and that of the encoded Na,K-ATPase alpha and beta subunits proteins, cannot predict that high level of Na,K-ATPase alpha nucleic acid subunit and low level of its beta nucleic acid subunit are indicative of risk of any cancer, including bladder cancer, because the data disclosed in the specification concerns risk of **recurrence** of bladder cancer, and cannot predictably apply to risk

of cancer, including bladder cancer. Risk of recurrence of bladder cancer is not the same as risk of any cancer, including bladder cancer, which encompasses a population of patients who **never had cancer**, but will have an increased risk of any cancer, including bladder cancer. Said population has different characteristics, such as different health level, and the outcome of which population is not predictably to be the same as those who previously had cancer.

Even if there were a correlation between the level of the encoding mRNAs and that of the encoded Na,K-ATPase alpha and beta subunits proteins, cannot predict that high level of Na,K-ATPase alpha nucleic acid subunit and low level of the beta nucleic acid subunit are indicative of risk of any cancer, including bladder cancer, in view of the following teaching in the art. Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to the claimed invention. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and **confirm marker predictive value in prospective population trials** (emphasis added) (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and **if validated** (emphasis added) can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and

link those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). Moreover, the need to perform validation studies when characterizing putative biomarkers is also confirmed by Oesterreich, S et al, 1996 (Clin Cancer Res, 2: 1199-1206, especially p. 1205, first column, last three lines of paragraph before last), who teach that false positive correlation can be obtained when using the univariate analysis to obtain a correlation of a marker with its prognostic value. Similarly, confirmation of prognosis ability of a marker protein is essential, in view of the teaching of Vandesompele J et al, 2003 (Oncogene, 22(3): 456-60). Vandesompele et al teach that the reported prognosis power of Id-2 expression in neuroblastoma cannot be confirmed, wherein Id-2 is assumed to be a direct target for MYCN protooncogene, the amplification of which is correlated with highly aggressive neuroblastoma. Thus without validation of the claimed method in a prospective population trial, one cannot predict that high level of Na,K-ATPase alpha nucleic acid subunit and low level of its beta nucleic acid subunit would be predictive of increased risk of bladder cancer.

Moreover, even if the claimed method could predict risk of bladder cancer, one cannot predict that the claimed method would predict risk of **any** cancer, because different cancers have different etiology and characteristics.

2. Claims 1-2, 4-5 are also rejected under 112, first paragraph, for lack of enablement for a method for analysis of a bladder carcinoma, by detecting high level of **variant** Na,K-ATPase alpha nucleic acid subunit and low level of its beta nucleic acid subunit.

The specification discloses that Na,K-ATPase alpha and/or beta subunits is any protein substantially similar to the amino acid sequence of the human polypeptide sequences of this family (p.6, first paragraph).

In view of the disclosure in the specification, Na,K-ATPase alpha and/or beta subunits encompasses variant Na,K-ATPase alpha and/or beta subunits.

Even if high level of Na,K-ATPase alpha nucleic acid subunit and low level of its beta nucleic acid subunit were predictive of increased risk of bladder cancer, one cannot predict that the claimed method using variant Na,K-ATPase alpha and beta nucleic acid subunits would be predictive of risk of cancer, including bladder cancer. It is well known in the art that variants of a sequence do not necessarily express at the same level as the corresponding wild type. For example, Schmid S et al, 2001 (J comparative Neurology, 430(2): 160-71), teach that the variants flip/flop of the gene GluR are expressed at higher levels in neurons in the auditory braistem, as compared to the wild type GluR-A and GluR-B, and that neurons in the central nucleus of the inferior collicullus express high levels of GluR-B flip but only low levels of the other receptor subunits. Conner et al, 1996 (Mol Brain Res, 42: 1-17), teach that full length trkB is found the hippocampus in patients with Alzheimer's disease, but not in hippocampi of either normal age-matched individual or patients with Huntington's disease, and that truncated trkB is found in senile plaques in hippocampus and temporal lobe in both patients with Alzheimer's disease and Huntington's disease, but not in normal brains of aged-matched individuals (page 8, item 3.1.2).

Thus in view of the teaching in the art one cannot predict the level of **variant** Na,K-ATPase alpha and beta nucleic acid subunits in bladder cancer. Consequently, one cannot predict that the claimed method using variant Na,K-ATPase alpha and beta nucleic acid subunits would be predictive of risk of cancer, including bladder cancer.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, LARRY HELMS can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS
March 06, 2008

/Larry R. Helms/

Supervisory Patent Examiner, Art Unit 1643